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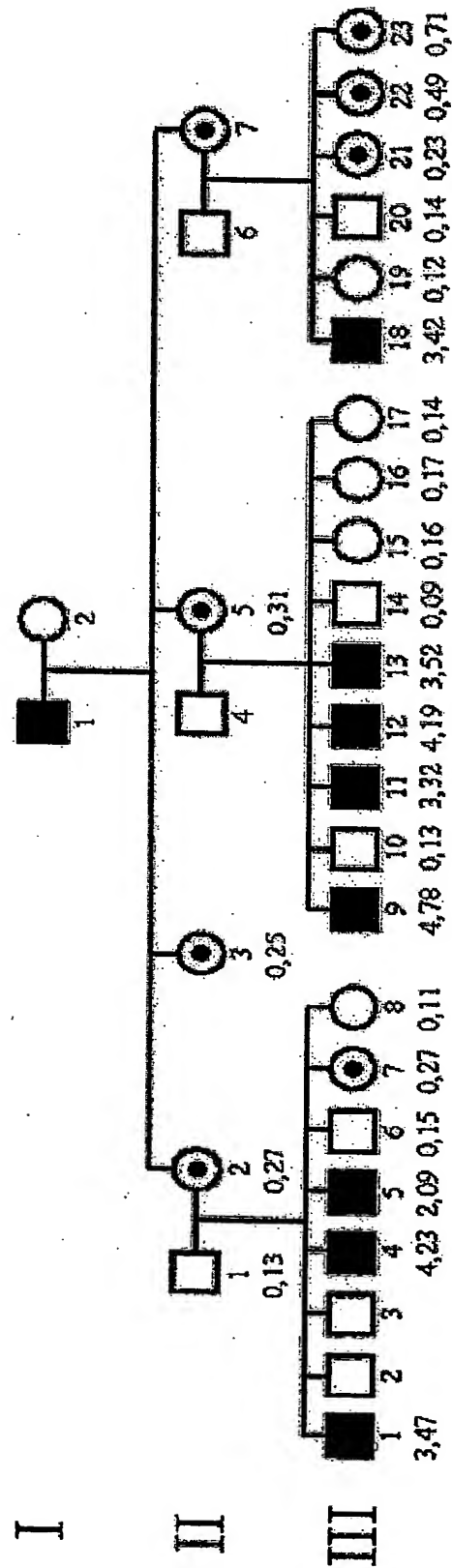


Figure 1A

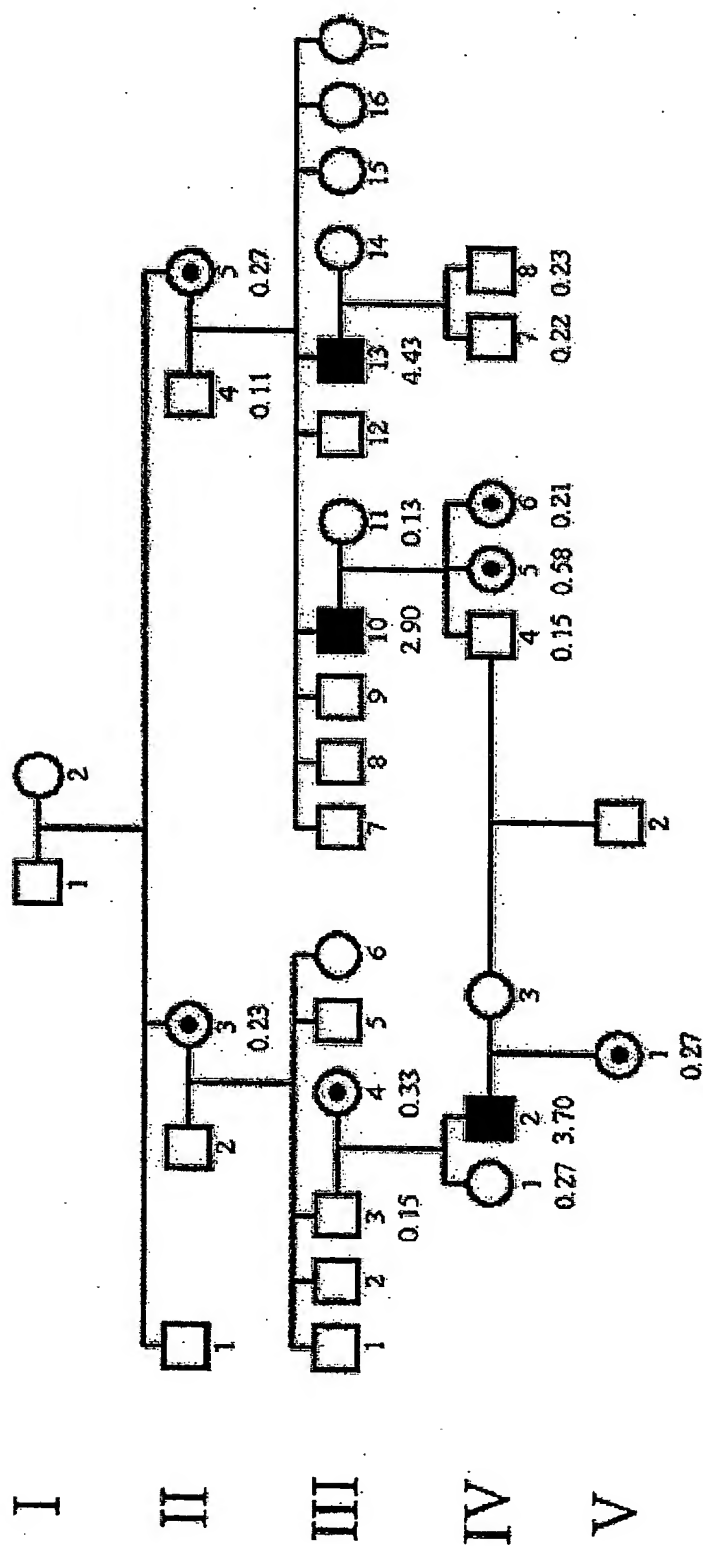


Figure 1B

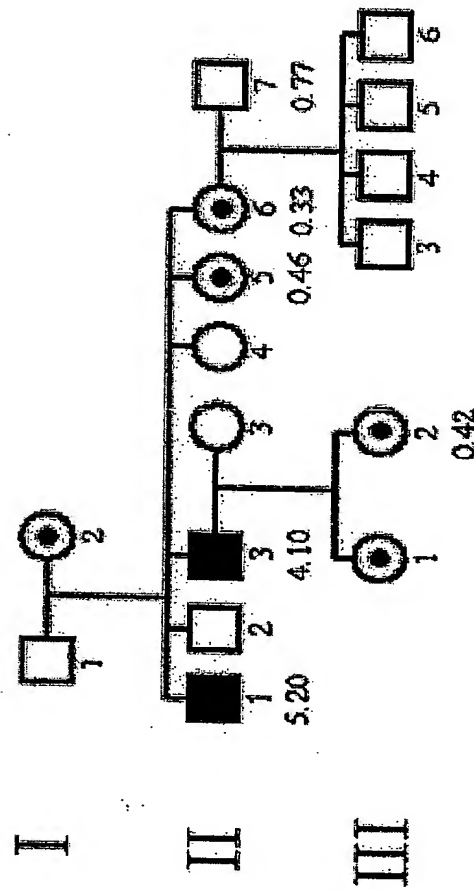


Figure 1C

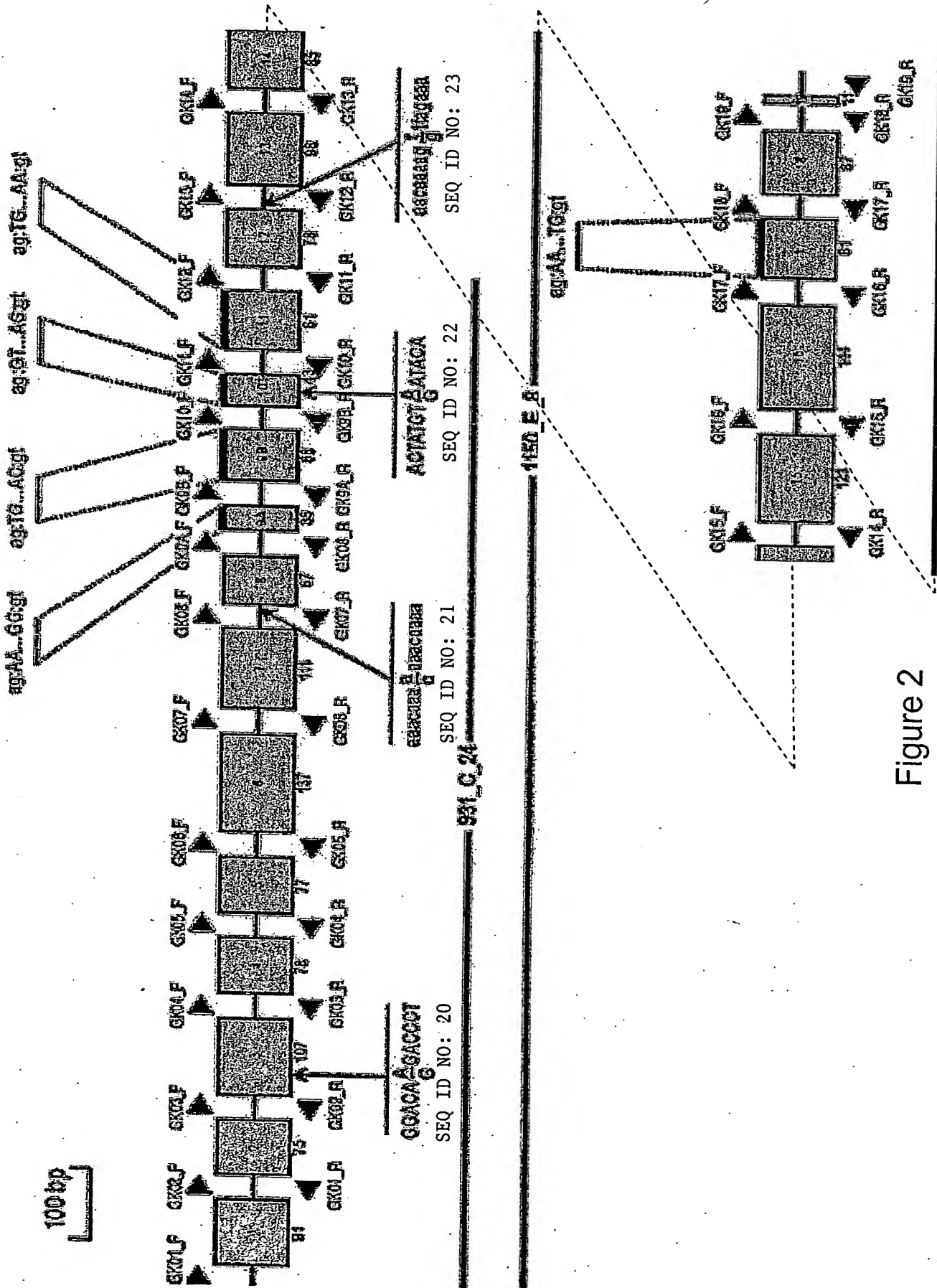
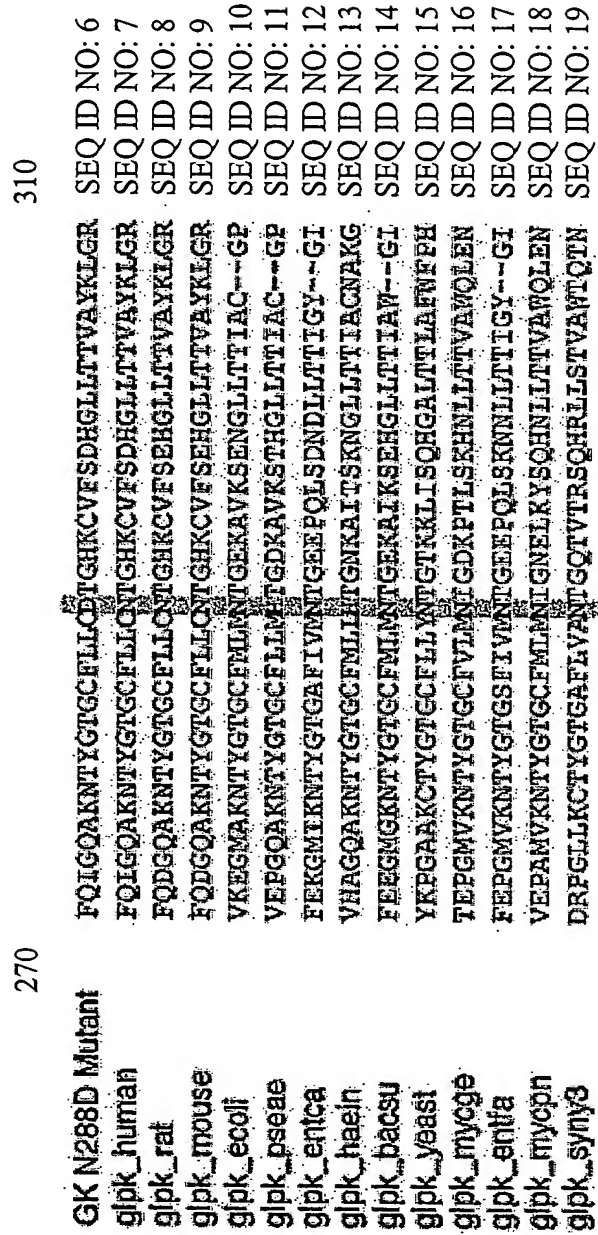
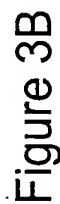


Figure 2



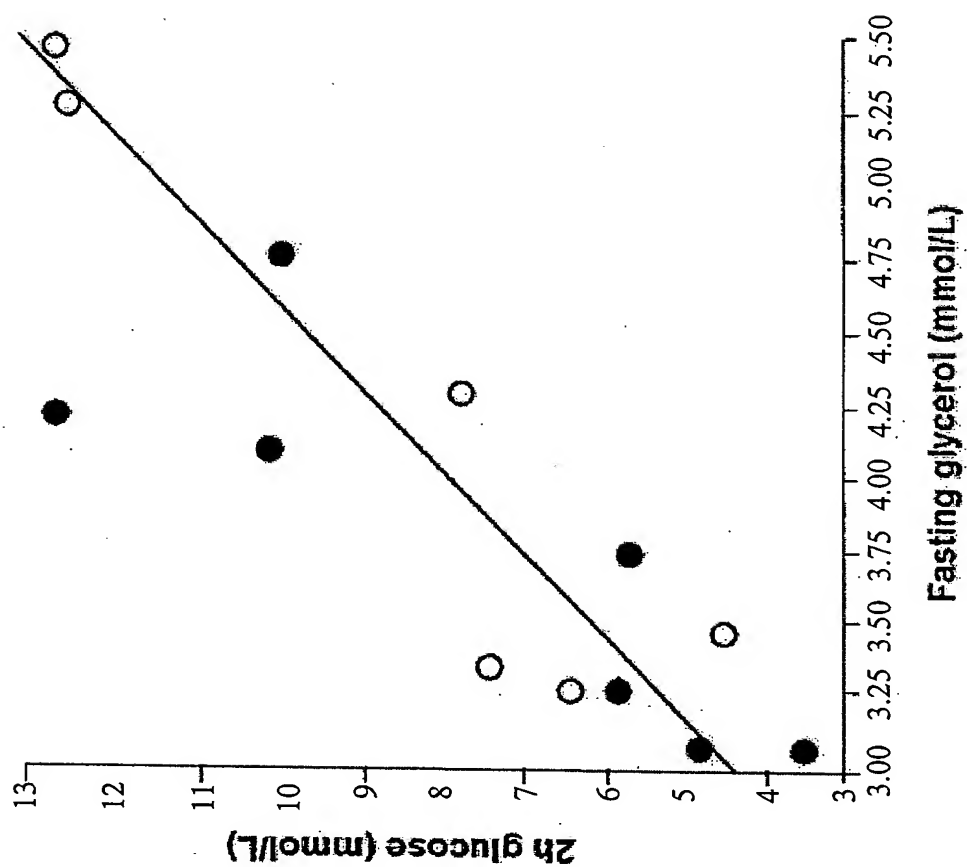


Figure 4A

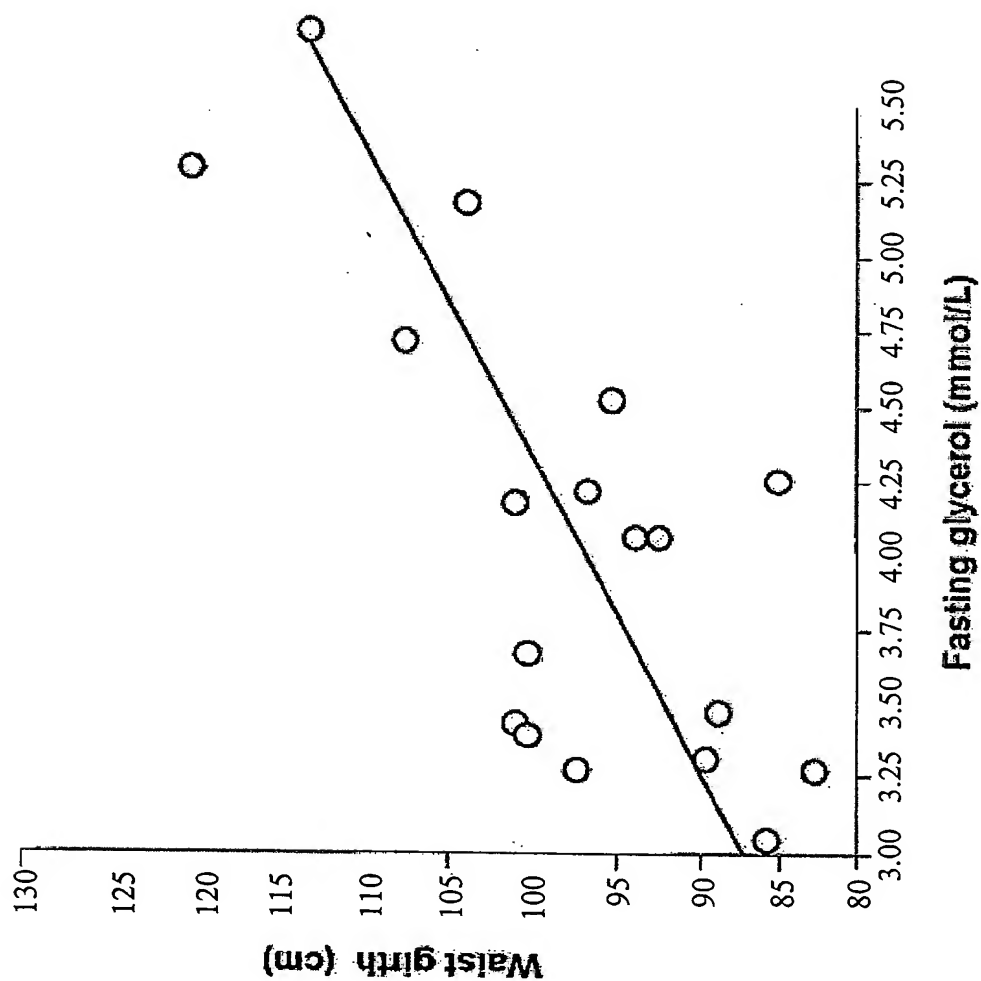


Figure 4B

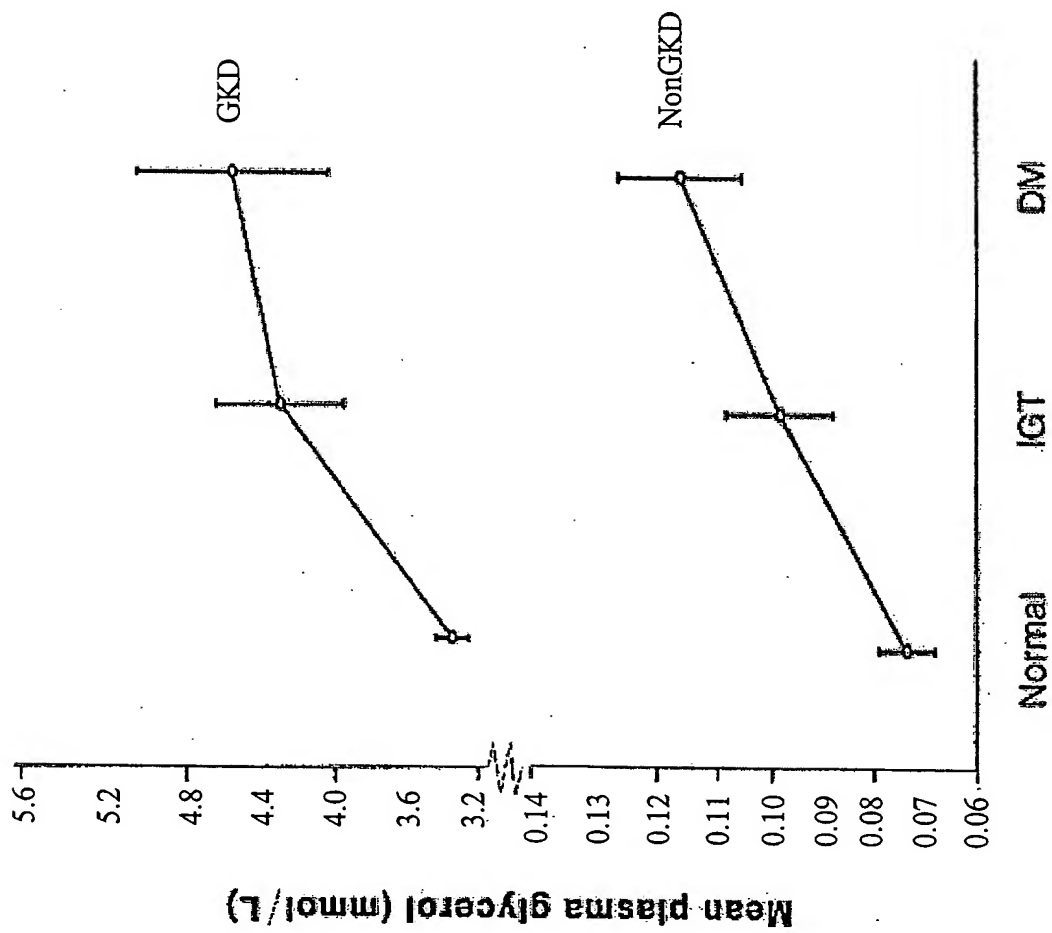


Figure 4C

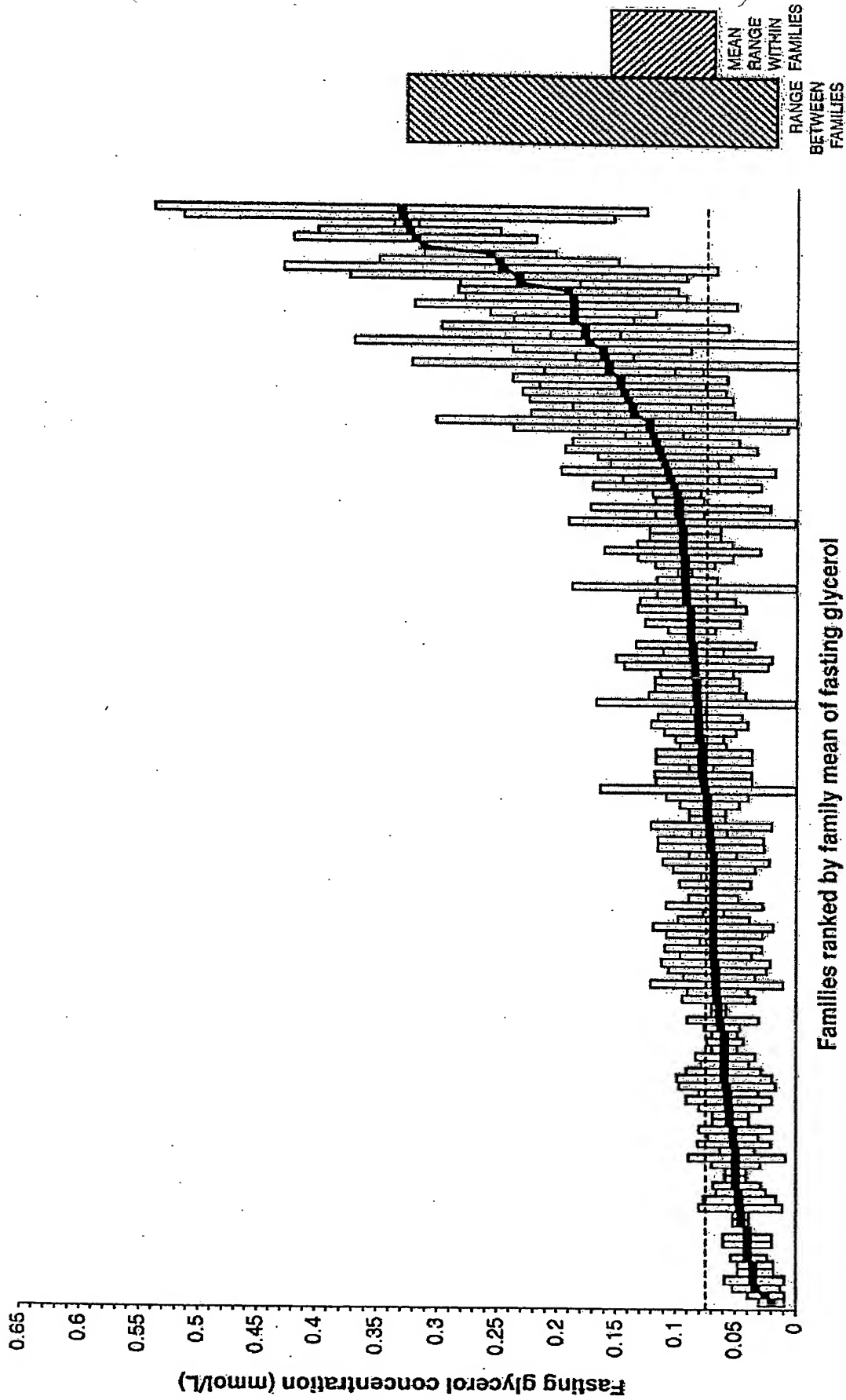


Figure 5

poly: A/G
location: 13th base of exon 3

ATGCCTTCTTTTGTCAAAGATGGGTGGAACA [A/G] GACCCTAAGGAAATTCTACAT
TCTGTCT SEQ ID NO: 1

CAA vs CAG ==> silent

poly: A/C
location: 17th base of intron 8

TAATGGTAAAAACAAACAAA [A/C] AAACAAAAACACACCAAAAAACCAA
SEQ ID NO: 2

poly: A/G
location: 29th base of exon 10

TTCATTCTCCCTTCAACCATAGGTATGGAACAGGATGTTTCTTACTATGT [A/G] AT
ACAGGCCATAAGGTtGGTTTTTAATAAAAATGATTAAGTCA SEQ ID NO: 3

AAT vs GAT ==> N to D

poly: G/T
location: 22nd base of intron 12

GAAATTGGTGAGTGTGTTCTAACAAAAG [G/T] TTAGAAAATCTGAAAATGACACA
TTTCA SEQ ID NO: 4

Figure 6

SEQ ID NO: 5

Exon 1:

GGTTCAGCGGACGCGCGCGGCCCTCGGTCTCTGGACTCGTCACCTGCCCCCTCCCCCTCCCGCC
GCCGTCACCCAGGAAACCGGCCGCAATCGCCGGCCGACCTGAAGCTGGTTTCATGGCAGCCT
CAAAGAAGGCAGTTTTGGGGCCATTGGTGGGGGCGGTGGACCAGGGCACCAGTTCGACGCGC
TTTTTGGTGAGCCCCGGGGTGACATGTGAAGAGGCGCTGAGC

Exon 2:

TGTAAAACGACGGCCAGTCATCCTTGATATCTGCCTGCATTTTTACATTAATATTACAATAT
CTTTTTCAGGTTTTCAATTCAAAAACAGCTGAACTACTTAGTCATCATCAAGTAGAAATAAA
ACAAGAGTTCCCAAGAGAAGGGTATGTTTCCTAATTTAATATGTAAAGACACATTATGTTTG
TTAGTCCATCTCACCCAACCTTGCCC

Exon 3:

CAATGCCTTCTTTTGTCAAAGATGGGTGGAACA [A/G] GACCCTAAGGAAATTCTACATTCT
GTCTATGAGTGTATAGAGAAAACATGTGAGAACTTGGACAGCTCAATATTGATATTTCCAA
CATAAAAGGTATTTTAGTAGAATATTTTACCCACA

Exon 4:

TGTAAAACGACGGCCAGTTGAGAGCTGTTTTCTGAAGTAGTTCCTACTTGTTAAATTTTTG
ACTTCCTTCTGTTTAACTTTCTCTTTAAAGCTATTGGTGTGAGCAACCAGAGGGGAAACCACT
GTAGTCTGGGACAAGATAACTGGAGAGCCTCTCTACAATGCTGTGGGTAAGCTGTCATGCAT
GGATGTCAAATGTAGGGCCTTTCTTCACATTGCAA

Exon 5:

TGTAAAACGACGGCCAGTTCCTTGATAGTGATTTTCAGTAAGTTCTTATTTTTTTTAAATGAAG
TTTTTCATGTATATTATTTTATTTTGGTCTATAGTGTGGCTTGATCTAAGAACCCAGTCTAC
CGTTGAGAGTCTTAGTAAAAGAATTCCAGGAAATAATAACTTTGTCAAGGTAAGAATTTCTT
CAGAAGTATACTATAAGAATGTTTCTTTTTTTAAAAAAAGTTTGCAGATTTCACTAGAAAGA
AGCATCTTATGGTACAATAGTTATTTGATACAATTTATAGAATCTTTTTTCCCGGATAATTGA
GGCC

Exon 6:

TGTAAAACGACGGCCAGTTTCTTTTGTGGTGGTTTTGTTTTAAACTGTTACACTTTTTCAT
TTGCTAACTGAACTTCACAACTGCTTTTAGTCCAAGACAGGCCTTCCACTTAGCACTTACTT
CAGTGCAGTGAACTTCGTTGGCTCCTTGACAATGTGAGAAAAGTTCAAAGGCCGTTGAAG
AAAAACGAGCTCTTTTTGGGACTATTGATTCATGGCTTATTTGGGTATGTTTAAATATAATG
GATATATGGAGAATTTTTTCAGAAATTTTTCTAGACTGCCTTGCCTATTGTTTCTACTAGC
AGGTCAGACTTTTTAATTAGCA

Figure 7A

Exon 7:

TGTAAAACGACGGCCAGTTGTGCTCTGCTGATTATGACCCTTAACAATATGTAAATTAAATT
GCCAATAAGTACAAATTTAACCTGATTTTTTTTACTCTGCCTAGAGTTTGACAGGAGGAGTCA
ATGGAGGTGTCCACTGTACAGATGTAACAAATGCAAGTAGGACTATGCTTTTCAACATTCAT
TCTTTGGAATGGGATAAACAACTCTGCGAGTAAGTTCTGTTTTGCTCTAAATATAGTTTTCC
CAATACACTACCTATTTTATAACCGAAATCTTAATATTTTCAGATGTCAGTGGAGCA

Exon 8:

TGTAAAACGACGGCCAGTACAGTGTTAAATACCCAATCTTCTTGTTTTTCAGATTTTTTTGGA
ATTCCAATGGAAATCTTCCAAATGTCCGGAGTTCTTCTGAGATCTATGGCCTAATGGTAAA
AAACAAACAAA [A/C] AAACAAAAAACACACCAAAAAACCAAAAAACAAACAAAAAAAACC
TAATAATTAAAGTTTTTTTTATTACAAAACAAGTTTACTATTCATAATTCAAAGTCAACTGT
GTTATGTTTTGTGACTTAAAACTTTACAGTCCTTTTTTACAATGG

Exons 9A and 9B

AAAGCTGGGGCCTTGGAAGGTGTGCCAATATCTGGGGTAAGTTTCATCACCAAGTGTCTCCC
CATCCCCACCCTTCCCCATGTTATGGCTTTCCTCCTCTTAGTTCATCAGTGTGCCTCTTTTT
AAACTAGGGAAAACAAGTAAAAGTTGCAAAATTGGANNNNTCTTGTTCTTACATGTCATACT
GTGGGCCATTGAGAATCTTTTGAATAAATTAATTTTAACTCTCCCTTCCCATACCTATTATC
TTACATATTAACAAATGGTATTAACAAATGGGGAAAATGGCCAAATGGAGAAAATGCAAGGA
AATAGACAGTTCATTCTTTGATAAATAAAAAATGAAAAATAAATCCTATGGCTCTTCTAAAA
AGAAAGTTAATACTATTGTATTAGTCAGTGTTCTTTATTGTCAATTATACCTTTCAGTGTTTA
GGGACCAGTCTGCTGCATTGGTGGGACAAATGTGCTTCCAGATTGGACAAGCCAAAAATAC
GTGAGTTTAAGAAACAGACTTAAAAACCAATGCTGTTTTGTGTTTTTCTACTTGGTGCTTTGA
ATAAGGAAAAGCTTTTTGAAGTTCATCCAGGATGAAAATCAATAGCTTAATAGCTCCAATATG
CATATATACACTTTTTTACCATTTTTTTTATATCTTTAAATAAAATACAAA
TGCCATATATATGCACACTGATGAAGCTTATAAAGACCTAAATTTGTAGGCTGGGCGCGG

Exons 10 and 11:

TTATTTGCTTTCAATAAAATTGTCTTCTATTTCATTCTCCCTTCAACCATAGGTATGGAACAG
GATGTTTCTTACTATGT [A/G] ATACAGGCCATAAGGTTGGTTTTTTTAAATTAAAAAATTGA
TTTAAAGTCTAAGTTCATCTAAATAATGCTTGAACATAATTTACTATTAAACAACCTTTTAG
TCTTTAGCTTTTACTTAATCTTTATCAGGGTTTAATTTAGAGCTCAATACAAAATTTGAATC
GTTCTAATAAGAACCATTTTAGACTCTTTGAATTTTATATGTGTGTTTTTAATTGTGCTGGG
GGGAAATCTAGACTGAGACCTCATCAAATCTTAATGCAATCTAATTTGAAACAAGGAATA
AACTTTTTTATACAGCTTAAATGTGTTCTTAATTCTGATCGTTTTTGACTGTAAGGATTTATTT
TAAAAATTGGTTTATTGATTGCATTATTTTGTACCTATGTTATTTTAACTTTAAAAAAAAGT
TCTCATGTTATCTTTTCATTTTCCACTACTGAAATCTTTTTTTTTTCTTTCTTACAGTGTGT
ATTTTCTGATCATGGCCTTCTCACCACAGTGGCTTACAACTTGGCAGAGACAAACCAGTAT
ATTATGCTTTGGAAGTAAGTTCTTTTAAATCAATATGGATAATATGACAAACATTCAAAGCT
AATAAAAATCACAGAGTTTTCTAACACTTTTCTGGTAAATCTTAATACAGAGGACTCAAAAA
GTTCTGCTTTCTTGGCATTGATTGAGTTGAAGGAACCTGAAACTGATCTGGGTGTCAGGAC
TCACAGGAGACCTTGATTAGATTGGTTCCTCAGTTCTTATGCCAATTAATCATGTACCTTA
GGCATATTACTTGAGAGCTCTACAATGTGAGGTTTTTTTTTTTTTATCTCTAAAGTTTAAAT
CGGATTAACGTGCTCTCTAACATTTCTTTCATCTTGAAAATCTTTGATTTTATAAATAAAA
TGCTCCAGTGTTCCAAAGAGAACCTGGGCACAAATAGGCAGAACAACTCTCTTCACTTGTC
TCCTCATAAAAATAAATTTTGTGTAACATTTTGATATAGAAAAGAAAGCGACGAGATTTATG
CCACTTATCACTGGAAACATTTGTTTCAAACATTTTTGTATGTTATAGTAGGAATATGCCAG
CCTAAGCCTATA

Figure 7B

Exon 12:

TTTTATTAGTGA CTTAGATAAAACTATGTTTGTATTAGAAAGACCTAGTTTACATATTTGTCTG
GAGTCTCAAAATGGAACTGAATTTCTGTCCATCTGATTGTGTCATACACAGAATATGCTCAA
TAAAAACCTTGGATAGTGATAAAATATATTCTGTCTTGAATTCCTTTTTTTCTTTAGGGTTC
TG TAGCTATAGCTGGTGTCTGTTATTCGCTGGCTAAGAGACAATCTTGGAATTATAAAGACCT
CAGAAGAAATTGGTGAGTGTGTTCTAACAAAAG [G/T] TTAGAAAATCTGAAAATGACACA
TTTCAGTATTTTATCTCTGCAAAGTAAATATCGATGCTTTGCCCAAATGTGAT

Exon 13:

CCAGTTGTGTGATTTTTGTTTTGTTTTGTTTTAATGTTAGAAAACTTGCTAAAGAAGTAGG
TACTTCTTATGGCTGCTACTTCGTCCCAGCATTTTCGGGGTAATATGCACCTTATTGGGAGC
CCAGCGCAAGAGGGTAAGTATTGAAAATATGGAGTGCTTTTGGGGATCTTGATTTAT

Exons 14 and 15:

TGTA AACGACGGCCAGTTGATTATGTCCAATTTTCTCTTCCTGGACATTTCTGTCTACCAA
ATTTGACCTTTTTCATATTTGAGATATTTCAAATTGATTGGTTTATATCATTCTAATCTGAAA
ATCTTTGTGCGTATTTTTAGGATAATCTGTGGACTCACTCAGTTCACCAATAAATGCCATAT
TGCTTTTGTCTGCATTAGAAGCTGTTTGTTCCAAACCTCGAGAGGTAACAAATATGGGCCTGT
TTTCTTGTACTTAGTTCACTTTTATCACTCTTAAGTTATATGTTAACACCCGAGATTTATTC
AGTACTGAAAATGTAGTTAATCAAATATTAAGGCTGCCTAAATACTAATCTAAATATAAGCA
GGGTTTTTCCCCCTTTTTCCAGCTGTCATTACCTTCTAAGTTCTGTTCCTGTTCAGGCACTG
GGAAATTTATGGTTGTGGGGAGGCTGAGTGGCACACATTAGGCAAAGGAAACAGCACAAACA
TAGGCATCaAGGCAGAAAAACAGGGTGCAAAATAGAGTTGTATAGCTTAGCTGAATATCAAG
GTGAATGCAGAGGTGTAGTGAGAGAAAAGGTTGGCTGTGACCAGATCAAAGAGGGCTTAGAA
GACCAGAATAAGAAGTCTCAATTTATTCCATAGGCTCTTGGAAGCTCTTGAGAGTTTCTGAG
TGGAGGATTGCCATTTTTCAGAGATGTTACTATGAAATAGATTTATAACATTAATTGCACTGG
TTTATTTAAGATTTTGGATGCCATGAATCGAGACTGTGGAATTCCACTCAGTCATTTGCAGG
TAGATGGAGGAATGACCAGCAACAAAATTCTTATGCAGCTACAAGCAGACATTCTGTATATA
CCAGTAGGTTAGTAAGTCTTCATTTCCTTTAAACTCCCAGAGTAATGTTTCTTGTGGAATAAC
TAGTTCCTTTGGG

Exon 16:

TGTA AACGACGGCCAGTTCCCAGAGTAATGTTTCTTGTGGAATAACTAGTTCTTTGGGCAT
ATGTAACCACAAAGATATTGATGGAACCTCTCTCTCCTCAGTGAAGCCCTCAATGCCCGAAAC
CACTGCACTGGGTGCGGCTATGGCGGCAGGGGCTGCAGAAGGAGTCGGCGTATGGAGTCTCG
AACCCGAGGATTTGTCTGCCGTCACGATGGAGCGGTTTGAACCTCAGATTAATGCGGAGGGT
ACATTTAAGAATGAAATGTTTCAGTGATATACTGTGAAAACGACCTTAGTGCACGGGAGTTT
TGTTTTTCTGTTTAGTTAAAAGTTAAGGAACCAAGTAAAATAGTAAATGTTATCATTGCAGA
TTCGGCTGCCAAGCATATTGGGCTTTACTGAATAAATGTGAATGAGAGAAATCGTTGCTTAT
CAAAAGAACTTCTAAAATCACTTTTTTAAAATCATT

Exon 17:

TGTA AACGACGGCCAGTAGCCCTACTGCAGTTTAATGTGTCAATAATTTGTCAAGAATGTT
GAGTGATCATAAGTATGGTACTAAGAACATCTCAGCAAACTACCTTTCGTTATGTGTTTTTT
CTACCTTCTAATTCTAGAAAGTGAAATTCGTTATTCTACATGGAAGAAAGCTGTGATGAAGT
CAATGGGTTGGGTTACAACCTCAATCTCCAGAAAGTGGAATAAATGTTTTTGTTTATTATTGT
CACATTTTCTTAGTATATTAAATAGTTATTTAAGTATCTAGGCATTTACACATAGCCAGGCT
GCTCTGAAGAAAAGCATTATCATATGTCCAGAGATTCTGACATTTTGAAAACACTTTAAAGT
TCTAAACACAAAATGTAAATTATCAGGTGT

Figure 7C

Exon 18:

TGTAAACGACGGCCAGTTGGTTTGGTTTGCTTGACTGGAATCTCTTCTGCTTGGATGACCA
CAGGTGACCCTAGTATCTTCTGTAGTCTGCCCTTGGGCTTTTTTATAGTGAGTAGCATGGTA
ATGTTAATCGGAGCAAGGTACATCTCAGGTTAGTTACTCTTTAAATTAGACAACTCTATTAG
TTAGCTTTAATGTTTTTCGTGTATAACTTAGCAGAAATTTTTCAGTGTTTTTCATTCTTTCTG
TGTCTAGGAAGCTGGAAAATCAATTAAAGGTCTAATTAGTTAGACCAATTAATCTTTGGGGG
CAGTTAGAAGTAAGAACTGTGACTCTGCTTACCCTTTTAAATTTTAAATGTGATGACTTCT
TTAAGAGGGACTACATTCTGCTGTCAGCTGCAGCAATAAGCAAAAGTGAAAATACTAATATT
TAAATGACAGGACTTTCAGACTGACTGCTGAAAGTTAAAGTATACTT

Exon 19:

AAAATTACTGGCTTAAATGGAAATGATGCTTCTTATTCTGTATGTTCCCATGAAAGTGAAAC
TTAAAAAATTCATGATTAGGGTTTCATGAAAAGGCCTTGTTTCTATGAAAATTGAGAC
AGGTTGCATCTCTCTAAGCTAAAAGATGGGCTATGTGTCTAGAGTCTTAGACTTCTAAAATG
CATGTGGTCACTATATGTAGGTTATCTCTTCGGTGACATACACTGCAATTTGAGAGGGCTGG
AAATTGTTTGCCTTGGTAAACGATTAGCAACAGTGGCAATATTTGTTAATTTTGGAATTGGC
CCTGTTTGTTCATTTTAATTGTGAGGCATGATTTAGAAATCATATGGACTTTCTAGCTTAA
TAAATGATTGAATCATCTGCATTGCTTTAACTCCTGAATTGTATGCATGTATTATTGACATA
TATGGTTTTTGTTCCTTCATTCAGGTATTCCATAAAACCTACCAACTCATGGATTCCCAAGA
TGTGAGCTTTTTACATAATGAAAGAACCCAGCAATTCTGTCTCTTAATGCAATGACACTATT
CATAGACTTTGATTTTATTTATAAGCCACTTGCTGCATGACCCTCCAAGTAGACCTGTGGCT
TAAAATAAAGAAAATGCAGCAAAAGAATGCTATAGAAATATTTGGTGGTTTTTTTTTTTTT
TAAACATCCACAGTTAAGGTTGGGCCAGCTACCTTTGGGGCTGACCCCTCCATTGCCATAA
CATCCTGCTCCATTCCCTCTAAGATGTAGGAAGAATTCGGATCCTTACCATTGGAATCTTCC
ATCGAACATACTCAAACACTTTTGGACCAGGATTTGAGTCTCTGCATGACATATACTTGATT
AAAAGGTTATTACTAACCTGTAAAAATCAGCAGCTCTTTGCTTTTAAAGAGACACCCTAAAA
GTCTTCTTTTCTACATAGTTGAAGACAGCAACATCTTCACTGAATGTTTGAATAGAAACCTC
TACTAAATTATTAAAAATAGACATTTAGTGTTCTCACAGCTTGGATATTTTCTGAAAAGTTA
TTTGCCAAAACCTGAAATCCTTCAGATGTTTTCCATGGTCCCACTAATTATAATGACTTTCTG
TCTGGGTCTTATAGGAAAAGATACTTTCTTTTTTCTTCCATCTTTCCTTTTTATATTTTTTA
CTTTGTATGTATAACATACATGCCTATATATTTTATACACTGAGGGAGCCCATTTATAAATA
AAGAGCACATTATATTCAGAAGGTTCTAACAGGG

Figure 7D

Table 1. Characteristics of Carriers of the N288D GK Gene Mutation and of Their Unaffected Relatives

	Men			Women		
	N288D carriers	Unaffected relatives	p	N288D carriers	Unaffected relatives	p
N	18	18		14	14	
Age (years)	46.4±14.2	42.0±18.8	0.32	44.9±13.5	43.7±17.8	0.87
Uncorrected triglyceride (mmol/L) ⁽¹⁾	6.26±1.13	2.05±0.54	<0.0001	2.84±1.20	1.30±0.65	0.0002
Glycerol (mmol/L)	3.99±0.71	0.10±0.04	<0.0001	0.54±0.14	0.10±0.02	<0.0001
Corrected triglyceride (mmol/L) ⁽¹⁾	2.27±0.75	1.95±0.53	<0.0001	2.31±1.22	1.19±0.67	0.03
Free fatty acid (mmol/L)	0.77±0.22	0.57±0.25	0.01	1.29±0.35	0.76±0.17	0.0004
Fasting glucose (mmol/L)	5.2±0.74	4.8±0.31	0.13	5.0±0.7	4.6±0.3	0.10
2h glucose following OGTT (mmol/L)	7.9±3.1	5.8±1.6	0.02	7.0±6.1	5.0±2.1	0.04
Fasting insulin (mU/L) ⁽¹⁾	13.3±14.0	15.1±14.8	0.62	12.2±13.1	9.0±3.4	0.60
Waist girth (cm)	97.7±9.3	88.1±12.3	0.01	88.5±3.8	79.8±5.8	0.03
Body mass index (kg/m ²)	27.9±4.1	24.9±3.9	0.03	28.1±5.5	23.1±2.3	0.001
%Total body fat	27.1±7.2	22.9±7.6	0.01	46.8±8.1	33.9±11.3	0.001

(1) Geometric mean, p after log transformation.

Figure 8

Table 2. Fasting plasma glycerol concentration (mmol/L) in the initial cohort of 1056 individuals, by risk factor of glucose intolerance and diabetes mellitus

		No.	Glycerol geometric mean \pm SD	p
Gender	men	717	0.065 \pm 0.081	<0.0001
	women - premenopausal	137	0.071 \pm 0.093	
	- menopausal	202	0.099 \pm 0.085	
Age (Y)	<50	486	0.071 \pm 0.082	0.0015
	50 - 60	408	0.076 \pm 0.106	
	>60	165	0.083 \pm 0.053	
Fasting glucose (mmol/L)	< 5.2	449	0.068 \pm 0.080	<0.0001
	5.2 - 5.9	336	0.070 \pm 0.090	
	6.0 - 6.9	271	0.090 \pm 0.100	
Fasting insulin (UI)	<15	637	0.067 \pm 0.082	0.02
	\geq 15	419	0.086 \pm 0.101	
2 hours glucose (mmol/L)	<7.8	572	0.062 \pm 0.071	<0.0001
	7.8 - 11.0	283	0.081 \pm 0.101	
	\geq 11.1	201	0.102 \pm 0.110	
Triglyceride (mmol/L)	\leq 2.2	389	0.057 \pm 0.062	<0.0001
	>2.2	667	0.082 \pm 0.103	
Free fatty acid (mmol/L)	< 0.6	589	0.066 \pm 0.054	<0.0001
	\geq 0.6	467	0.111 \pm 0.112	
Body mass index (kg/m ²)	\leq 27	428	0.060 \pm 0.087	<0.0001
	>27	628	0.079 \pm 0.097	

p value from a one-way ANOVA

Figure 9

Table 3. Multivariate analysis of the relationships of fasting plasma glycerol concentration with impaired glucose tolerance (2h glucose 7,8-11,0 mmol/L following a 75 g oral load) before and after adjustment for covariates identified in

	Model 1	Model 2	Model 3	Model 4
Glycerol (log)				
β	1.75	1.62	1.46	0.77
Odds ratio	5.76	5.42	4.33	2.46
p	<0.0001	<0.0001	<0.0001	0.01
Triglyceride (log)				
β		0.54	0.35	0.12
Odds ratio		1.75	1.42	1.12
p		0.02	0.11	0.63
Body mass index (kg/m²)				
β			0.10	0.05
Odds ratio			1.10	1.05
p			<0.0001	0.01
Fasting insulin (log)				
β				0.57
Odds ratio				1.31
p				0.39
Fasting glucose (mmol/L)				
β				1.13
Odds ratio				2.65
p				<0.0001
Free fatty acid (log)				
β				1.62
Odds ratio				4.33
p				0.007

Figure 10